Scaling of brain compartments to brain size

Jäncke, Lutz ; Liem, Franziskus ; Mérillat, Susan

Abstract: In this study, we examine the relationship between total brain volume (BV) and the volumes of several main brain compartmental (BC) measures (cortical thickness, cortical surface area, corpus callosum, cortical gray matter, normal appearing cerebral white matter (NAWM), amygdala, accumbens, caudate, hippocampus, putamen, pallidum, thalamus, cerebellar gray matter, and cerebellar WM) of physically and cognitively healthy elderly individuals (mean age: 71 years, age range: 65-85 years). The statistical analysis uncovered extremely different relationships between total BV and the aforementioned BC metrics. These relationships ranged from extremely strong (BV explaining 85% of the variability of cerebral WM volume) to a very small relationship (for the caudate volume and the cortical thickness). In addition, cerebral WM and the accumbens volumes scaled out of proportion with BV, whereas most other BC measures scaled less than proportional to BV. Thus, larger brains exhibit relatively larger cerebral NAWM and accumbens volumes than do smaller brains. Cortical gray matter (and most other BC measures), on the other hand, relatively decreases as BV increases, resulting in relatively small cortical gray matter volumes (and relatively small BC measures) for large brains. These relationships are discussed within the context of general allometric scaling principles for the human brain. In addition, possible methodological consequences of analyzing anatomical data on the basis of MRI measurements are also discussed.

DOI: https://doi.org/10.1097/WNR.0000000000001249

Scaling of brain compartments to brain size

Lutz Jäncke[a], Franz Liem[a,b] and Susan Merillat[a,b]

In this study, we examine the relationship between total brain volume (BV) and the volumes of several main brain compartmental (BC) measures (cortical thickness, cortical surface area, corpus callosum, cortical gray matter, normal appearing cerebral white matter (NAWM), amygdala, accumbens, caudate, hippocampus, putamen, pallidum, thalamus, cerebellar gray matter, and cerebellar WM) of physically and cognitively healthy elderly individuals (mean age: 71 years, age range: 65–85 years). The statistical analysis uncovered extremely different relationships between total BV and the aforementioned BC metrics. These relationships ranged from extremely strong (BV explaining 85% of the variability of cerebral WM volume) to a very small relationship (for the caudate volume and the cortical thickness). In addition, cerebral WM and the accumbens volumes scaled out of proportion with BV, whereas most other BC measures scaled less than proportional to BV. Thus, larger brains exhibit relatively larger cerebral NAWM and accumbens volumes than do smaller brains. Cortical gray matter (and most other BC measures), on the other hand, relatively decreases as BV increases, resulting in relatively small cortical gray matter volumes (and relatively small BC measures) for large brains. These relationships are discussed within the context of general allometric scaling principles for the human brain. In addition, possible methodological consequences of analyzing anatomical data on the basis of MRI measurements are also discussed. *NeuroReport* **30:573–579**

NeuroReport 2019, **30**:573–579

Keywords: allometric scaling, brain size, brain compartments, freesurfer

[a]Division Neuropsychology, Institute of Psychology and [b]University Research Priority Program 'Dynamics of Healthy Aging', University of Zurich, Zurich, Switzerland

Correspondence to Lutz Jäncke, PhD, Institute of Psychology, Division Neuropsychology, University of Zurich, Binzmühlestrasse 14/25, CH-8050 Zurich, Switzerland
Tel: +41 446 357 400; fax: +41 446 357 409; e-mail: lutz.jaencke@uzh.ch

Received 19 March 2019 **accepted** 20 March 2019

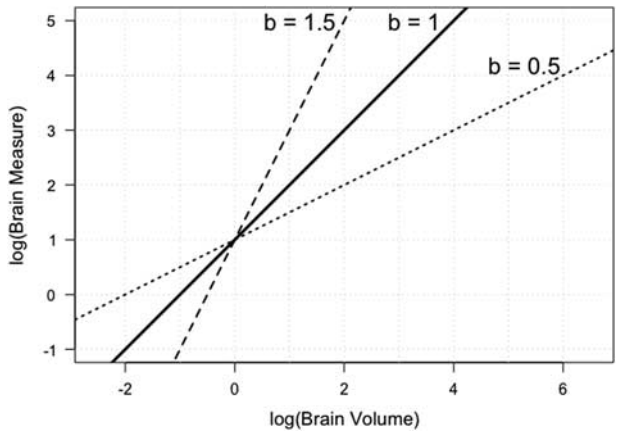
Introduction

With modern imaging techniques, the size of the brain can be measured *in vivo* using different parameters. For example, the volumes of different brain areas [e.g. intracranial volume (ICV), the volume of total brain tissue, and volumes of brain compartments] can be precisely measured *in vivo* using structural MRI measurements and appropriate analysis tools. The measured parameters vary considerably among individuals [1–3]. In healthy adult men, for example, ICVs range between 1 and 2 l, whereas in healthy adult women, ICVs are considerably smaller and range between 0.8 and 1.3 l. Comparable variabilities have also been found for total brain tissue volume. In adult men, brain tissue volume varies between 0.8 and 1.3 l, whereas in women this range is slightly smaller, between 0.7 and 1.2 l. Thus, questions arise with regard to how the volumes of the brain compartments [e.g. corpus callosum, cortical gray matter, cerebral white matter (WM), basal ganglia, thalamus, and cerebellum] scale as a function of total brain size. The compartmental volumes can theoretically vary in proportion, out of proportion, or less than proportional than brain size (Fig. 1). Moreover, it is necessary to determine whether and how the brain compartments vary with regard to this scaling. It is possible that several brain compartments strongly vary with brain size, whereas others do not. To the best of our knowledge, these questions have not yet been studied extensively.

How individual brain compartments scale in relation to total brain volume (BV) is not only of theoretical interest, but it has also several practical implications. It is particularly important to understand the scaling of brain compartments in relation to BV within the context of statistical analyses of neuroanatomical measures. Indeed, this is particularly important for comparisons between groups of people with different brain sizes as, for example, in neuroanatomical studies comparing men and women. Such sex comparisons raise the question of whether and how differences in the volume of brain compartments are predominantly caused by total brain size [1,3–7]. In such studies, BV is often used as a covariate, or the brain compartments are normalized linearly on the basis of BV [yielding to proportional brain compartmental (BC) measures]. This raises the question of whether a proportional adjustment of the brain compartment volumes to total BV is justified in all cases. If the brain compartments scale less than proportionally to BV, a linear downscaling of the volumes of the brain compartments would lead to overcompensation. However, if an out-of-proportion relationship between BV and the volume of the brain compartments exists, a linear normalization would lead to an under-compensation of their volumes. Basically, similar problems arise when applying the available techniques for stereotactic normalization within the context of voxel-based morphometry analyzes [8,9]. Indeed, these techniques do not account for specific relationships between brain size and BC volumes.

DOI: 10.1097/WNR.0000000000001249

Fig. 1



Hypothetical relationships between brain volume and compartmental measures. Shown are linear relationships between the log-transformed values with different slopes. A slope with a $b = 1$ indicates a proportional relationship between brain volume and the particular brain compartmental measure. A slope with a $b = 1.5$ indicates an out of proportion relationship and a slope with a $b = 0.5$ a less than a proportional relationship.

In addition to these statistical and methodological aspects, we can also learn about the basic architectural principles of the human brain from the brain size and the BC relationship. For example, are large and small brains similarly structured, or is a large brain simply a linearly up-scaled brain (regardless of sex)? In recent studies, it has been revealed that large brains (regardless of sex) show relatively smaller proportions of gray matter [1,3,5]. Other studies have shown that larger brains show stronger intrahemispheric and weaker interhemispheric anatomical connectivities, independent of sex [4].

In this study, we are readdressing and extending the questions of how and whether several brain compartments are related to brain size. Extending previous research, we are interested in studying the relationship between total brain size and several compartmental brain size measures. In particular, we will examine whether and how volumes of cortical gray matter, cerebral WM, cerebellar gray and WM as well as volumes of smaller compartments (i.e. basal ganglia, amygdala, hippocampus, thalamus, and corpus callosum) scale in relation to overall brain size. We also examine whether and how cortical surface area (CSA) and cortical thickness (CT) are related to overall brain size. A further study question focuses on the relationship between ICV and total brain tissue volume. As this relationship has rarely been examined, we know very little about how strong both brain measures is interrelated. As previously noted in an earlier paper [1], we argue that ICV, which is most likely strongly genetically determined, might provide a global and stable frame for the development of brain tissue, whereas the brain tissue itself is subject to change because of plasticity, disease, or aging [10–12].

As, to our knowledge, no study has thus far examined how the aforementioned brain compartments scale to brain size, we cannot formulate explicit hypotheses. The only exception pertains to the relationship between brain size, cortical gray matter, cerebral WM, and the corpus callosum because extensive information on these issues is available [1,3,4,13,14]. We assume that the cortical gray matter volume will scale less than proportional to brain size, resulting in relatively small cortical grey matter volumes for larger brains. A similar relationship is proposed for the corpus callosum, for which we identified relatively smaller corpus callosum areas with larger brain sizes. For cerebral WM, we hypothesize an out of proportion increase with larger cerebral WM volumes with larger brain sizes.

Participants and methods

Participants

Data were taken from the Longitudinal Healthy Aging Brain (LHAB) database – an ongoing project carried out at the University Research Priority Program 'Dynamics of Healthy Aging' of the University of Zurich [15]. The data of this sample have been used in previous publications of our group [1,16–19]. Thus, we only shortly reiterate the sample description. We used the LHAB data from the first (baseline) measurement (in total we measured the participants four times over a period of 4 years) that took place between 2011 and 2013. This data set included 231 participants (mean age = 70.8 ± 5.1 years; 49% female). In this paper, we will not report the results with respect to the longitudinal data set; we will rather focus on the first wave of data acquisition. Several papers have been published by our group presenting the longitudinal anatomical and functional changes [16–22]. All participants completed an extensive battery of neuropsychological tests and underwent brain imaging (functional and structural MRI). Eligibility criteria for study participation were age older than or equal to 64 years, a score of at least 26 on the Mini-Mental State Examination [23], consistent right-handedness (as confirmed by the Annett Handedness Questionnaire [24], German language proficiency, and no self-report of any neurological or psychiatric disease or other contraindications to MRI). The study was approved by the ethical committee of the canton of Zurich. Participation was voluntary and all participants provided written informed consent in accordance with the declaration of Helsinki. Participants of the LHAB sample are well-educated and general intelligence is above average as compared with the general population. General intelligence was measured with a standard German intelligence test (Leistungsprüfsystem), which is based on the Thurstone's intelligence model [25]. Here, we used the version for participants older than 50 years up to 90 years. The split-half reliability of this test ranges between $r = 89$ and 97 depending on the particular subtest. The detailed

Table 1 Age, and IQ for the participants broken down for sex

	Female		Male		All	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	70.7	5.1	70.9	5.1	70.8	5.1
IQ[a]	119.4	5.9	121.7	7.3	120.6	6.7
Education in (years)	13.3	3.0	15.8	3.7	14.6	3.6
Education (degree)	4.03	1.2	4.7	1.2	4.3	1.3
Body height	164.6	5.9	175.9	5.9	170.3	8.2

[a]IQ could be slightly overestimated as the participants mostly fall exactly in the age range between two age categories (55–69 and 70–90 years). We have used the normalization for the age category 70–90 years. In addition, the statistics for the entire sample (all) are also shown.

data for age, body height, and IQ are shown in Table 1. Subsequently performed *t*-tests revealed that age was similar for both men and women. However, men and women differed with respect to IQ, education in years, education degree (0: no formal education, 5: academic education), and body height, with men showing higher values than women.

Image acquisition

MRI data were acquired with a 3.0T Philips Ingenia scanner (Philips Medical Systems, Best, the Netherlands). We have described the image acquisition procedure in several of our recent papers; thus, we only shortly reiterate the technical details [1,17–19] (T1-weighted images, recorded with a gradient echo sequence; three-dimensional turbo field echo, 160 sagittal slices, slice thickness = 1 mm, in-plane resolution = 1 × 1 mm, field of view = 240 × 240 mm, repetition time = 8.18 ms, echo time = 3.80 ms, flip angle = 8°). FreeSurfer v5.3 (*https://surfer.nmr.mgh.harvard.edu*) was used to obtain measurements of cortical and subcortical anatomy [26–29]. After completing the standard *recon-all* pipeline, measurements for CT, surface area, and volumes were extracted for the regions of the Destrieux (*aparc.a2009s*) parcellation scheme [26]. Subcortical and global volume measurements were also extracted from FreeSurfer's *aseg* segmentation. The *aseg* procedure is described in detail in the seminal paper of Fischl *et al.* [28]. This segmentation procedure has meanwhile been used by many groups worldwide and has been proven to result in valid anatomical estimates. This procedure revealed the following anatomical measures:

(1) Intracranial volume (ICV) representing the head size.
(2) Total brain volume without ventricles, cerebrospinal fluid, and choroid plexus (BV).
(3) Mean cortical thickness (CT): CT is calculated as the distance between the white and pial surface after tessellation of the gray and WM boundary and topology correction.
(4) Total cortical surface area (CSA).
(5) Total cortical grey matter volume (CortexVol): this is the volume inside the pial surface minus the volume inside the white surface minus tissue inside the ribbon that is not part of the cortex (e.g. hippocampus).
(6) Total cerebral normal-appearing white matter volume (NAWM): this is volume inside the white surface minus anything that is not WM. It does not include cerebellar WM or brainstem. The volume of the white matter hyperintensities (WMH) is subtracted from the cerebral white matter count.
(7) Corpus callosum volume (CC): this is a three-dimensional segmentation of the callosum that provides a volume measurement, which strongly correlates with the midsagittal callosum area [30].
(8) Cerebellar gray matter volume (CBGM).
(9) Cerebellar white matter volume (CBWM).
(10) Accumbens volume (Accumbens).
(11) Amygdala volume (Amygdala).
(12) Caudate volume (Caudate).
(13) Pallidum volume (Pallidum).
(14) Putamen volume (Putamen).
(15) Hippocampus volume (Hippocampus).
(16) Thalamus volume (Thalamus).

In the following, the brain metrics listed from (3) to (16) are denoted as BC measures.

Statistical analysis

To estimate the relationship between BV and the BC metrics, linear regressions were computed between the particular BC measure as the dependent variable and BV as an independent variable. The least squares regression analysis was computed on the logarithmic transformation of both the dependent variable (y) and the independent variable (x) yielding the linear relationship:

$$\log y = \log a + b \log x,$$

where a is the y intercept and b is the slope. This log–log transformation is convenient in that it usually fits the data. In these linear relationships, the slope b is the scaling factor [13,31]. In relationships in which a change in the independent variable is less than proportional $b < 1$, in case of proportional scaling $b = 1$, and when the change is greater than the change in brain size $b > 1$. Besides the slopes, R^2 statistics were also computed to estimate the amount of variance of the dependent variables (BC measure) explained by the independent variable (BV). To test whether the obtained slopes differ from proportionality the *linearHypothesis* tool from the *R package* was used. Before log transformation, all brain measures are corrected for age, sex, and ICV using linear regression analyses.

To statistically evaluate whether the different brain compartments differ with respect to their relationship with BV, we conducted a multiple regression analysis with the different brain metrics as independent variables and BV as the dependent variable. To estimate the relative importance of each predictor in explaining the

variability of BV, we used the *relaimpo* software tool using the *lmg* metric providing a decomposition of the model-explained variance into non-negative contributions of each predictor [32]. On the basis of bootstrap analyses, we tested whether a particular R^2 value (estimated by the *lmg* metric) deviated from 0 and whether the R^2 value for the different regressors differs from each other. Before the statistical analyses, the necessary assumptions for applying linear regressions (i.e. the approximately normal distribution of the residuals, homoscedasticity) were confirmed for the present data set. All statistical analyses were carried out with routines from the R software [33] on a MacBook Pro.

Results

The means and SDs of all brain metrics are shown in Table 2 broken down for men and women. Table 3 shows the results of the linear regression analyses with log BV as a predictor and the BC measures as dependent variables. As one can see from this table, there are significant relationships between BV and all BC measures. The descriptively strongest linear relationships were found for NAWM ($R^2 = 85\%$), CSA ($R^2 = 77\%$), and CortexVol ($R^2 = 73\%$). The weakest was identified for the Caudate ($R^2 = 5\%$) and CT ($R^2 = 10\%$). A clear out of proportion relationship (indicated by $b > 1$) was found for the Accumbens ($b = 1.22$) and the NAWM ($b = 1.19$). The relationships between the Amygdala and the CC with BV were perfectly proportional (Amygdala: $b = 1.02$; CC: $b = 1.07$). The other brain compartments are all associated with slopes less than 1 indicating a less than the proportional relationship to BV. The also calculated regressions between BV and ICV (both sex and age-corrected and log-transformed) revealed a significant linear relationship (R2 = 0.34, intercept = 4.5 and b = 0.33).

Table 2 Average brain metrics and SDs broke down for sex

	Female		Male		All	
	Mean	SD	Mean	SD	Mean	SD
ICV	1346.9	197.7	1584.4	199.1	1468.2	231.0
BV	981.8	75.9	1085.5	88.4	1034.8	97.4
CT	0.4	0.0	0.4	0.0	0.4	0.0
CSA	3.1	0.0	3.2	0.0	3.1	0.0
CortexVol	403.7	31.8	442.9	32.7	423.7	37.7
NAWM	406.7	40.7	454.1	51.1	430.9	51.9
CC	3.0	0.5	3.1	0.6	3.0	0.5
CBGM	92.9	8.3	103.8	9.7	98.5	10.5
CBWM	26.5	3.5	27.8	4.0	27.2	3.8
Accumbens	0.8	0.2	0.9	0.2	0.9	0.2
Amygdala	2.8	0.4	3.2	0.4	3.0	0.4
Caudate	6.6	0.9	7.2	0.8	6.9	0.9
Hippocampus	7.4	0.8	7.8	0.9	7.6	0.9
Pallidum	3.4	0.4	3.6	0.5	3.5	0.4
Putamen	8.4	1.0	9.3	1.0	8.8	1.1
Thalamus	12.2	1.0	13.5	1.2	12.9	1.3

Volumes are shown in cm^3, CT in mm, and CSA in cm^2.
Accumbens, accumbens volume; Amygdala, amygdala volume; BV, brain volume; Caudate, caudate volume; CBGM, cerebellar gray matter volume; CBWM, erebellar white matter volume; CC, corpus callosum volume; CortexVol, cortical grey matter volume; CSA, cortical surface area; CT, cortical thickness; Hippocampus, hippocampus volume; ICV, intracranial volume; NAWM, cerebral normal-appearing white matter volume; Pallidum, pallidum volume; Putamen, putamen volume; Thalamus, thalamus volume.

Table 3 Results of the linear regressions between these log-BC measures as dependent variables (*y*) and the log-BV measure as an independent variable (*x*)

	R^2	Intercept	Slope	$b < 1 / > 1$	*t*	*P*
CT	0.10	0.02	0.12	***	5.05	***
CSA	0.77	1.65	0.81	***	8.17	***
CortexVol	0.73	0.48	0.80	***	24.77	***
NAWM	0.85	−2.17	1.19	***	36.24	***
CC	0.29	−6.34	1.07	NS	9.71	***
CBGM	0.32	0.13	0.64	***	10.26	***
CBWM	0.30	−2.35	0.81	*	10.02	***
Amygdala	0.44	−6.02	1.02	NS	13.47	***
Accumbens	0.30	−8.62	1.22	*	9.84	***
Caudate	0.05	−0.10	0.29	***	3.43	***
Hippocampus	0.50	−4.02	0.87	***	15.02	***
Pallidum	0.19	−2.84	0.59	***	7.42	***
Putamen	0.15	−1.47	0.52	***	6.46	***
Thalamus	0.48	−2.56	0.74	***	14.67	***

Indicated are the R^2 values, the intercept of the regression equation, the slope (which is the scaling factor), the test result for examining whether the slope is different from 1 and thus different from proportionality, the *t* value of the regression.
Accumbens, accumbens volume; Amygdala, amygdala volume; BC, brain compartmental; BV, brain volume; Caudate, caudate volume; CBGM, cerebellar gray matter volume; CBWM, erebellar white matter volume; CC, corpus callosum volume; CortexVol, cortical grey matter volume; CSA, cortical surface area; CT, cortical thickness; Hippocampus, hippocampus volume; NAWM, cerebral normal-appearing white matter volume; Pallidum, pallidum volume; Putamen, putamen volume; Thalamus, thalamus volume.
*$P < 0.01$.
***$P < 0.001$.

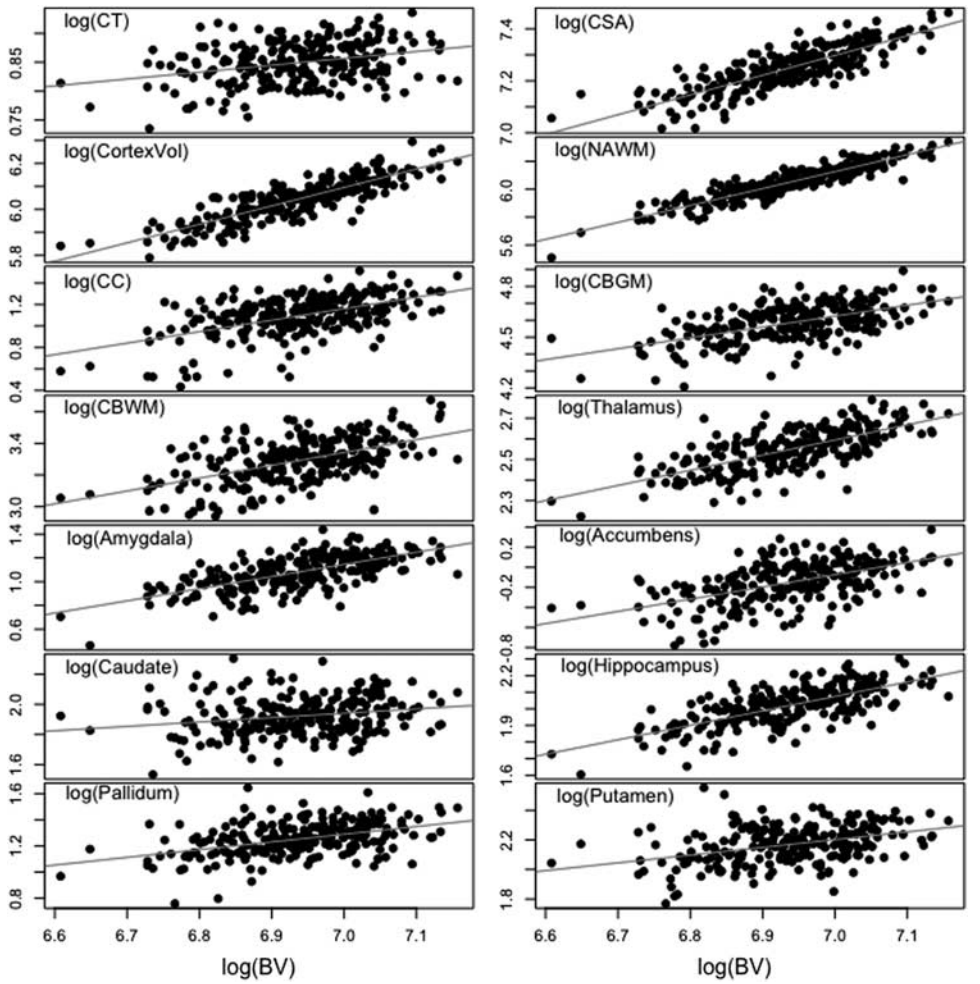
The plotted relationships are shown in Fig. 2. As one can see from this figure all relationships are linear. In addition, performed regression analysis with nonlinear trends revealed no nonlinear relationship.

The relative importance of each brain measure for explaining BV is shown in Fig. 3. Shown is the relative importance for each brain measure as a percent of the totally explained variance of the multiple regression analysis with all brain compartment measures as the independent variable and BV as the dependent variable (adjusted $R^2 = 99\%$). In addition, performed randomization tests revealed that NAWM explained 23% of the entire BV variance and is thus the brain compartment measure most strongly related to BV. CortexVol and CSA explain 16 and 14% of the BV variance and, thus, are the second most strongly associated brain compartments. Thalamus, Hippocampus, Amygdala, CBGM, CBWM, CC, and Accumbens are only weakly related to BV explaining variances ranging between 7.1 (Hippocampus and Thalamus) and 3.8% (Accumbens). Pallidum, Putamen, and Caudate are those brain compartments most weakly related to BV (2.4% for the Putamen, 0.6% for the Caudate). The relative contributions are shown in Fig. 3.

Discussion

The aim of the present paper was to examine the relationship between brain size (here BV) and several BC measures. As expected, all BC measures are significantly

Fig. 2



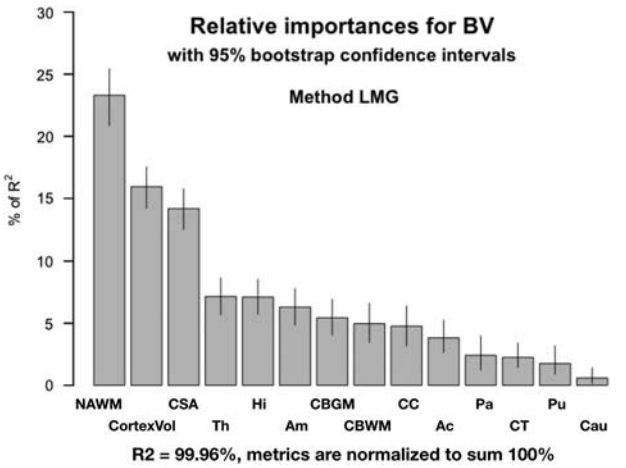
Scatterplots for the relationship between brain volume (BV) and the different brain compartment (BC) measures. Shown are also the fitted regression lines. CT is measured in mm, volumes are measured in cm^3, and CSA in cm^2. Accumbens, accumbens volume; Amygdala, amygdala volume; Caudate, caudate volume; CBGM, cerebellar gray matter volume; CBWM, erebellar white matter volume; CC, corpus callosum volume; CortexVol, cortical grey matter volume; CSA, cortical surface area; CT, cortical thickness; Hippocampus, hippocampus volume; NAWM, cerebral normal-appearing white matter volume; Pallidum, pallidum volume; Putamen, putamen volume; Thalamus, thalamus volume.

related to BV. However, the relationships vary considerably among the different BCs. The strongest relationship with BV was identified for NAWM, CSA, and CorticalVol. More than 73% (even 85% for NAWM) of the variability of these BCs is statistically explained by BV. The relationships with the other BCs are much lower. For example, ~50% of the variability of the Thalamus ($R^2 = 48\%$) and the Hippocampus ($R^2 = 50\%$) volumes are statistically explained by the variability of BV. For the basal ganglia, the Amygdala was strongest related to BV, whereas the Accumbens, Putamen, Pallidum, and Caudate were less stronger related to BV. Especially, Pallidum, Putamen, and Caudate are weakly related to BV ($R^2 =$ 5–19%). CBWM matter and CBGM are moderately related to BV with R^2 values ranging from 30 to 32%. Finally, the CC is also moderately related to BV ($R^2 = 29\%$). Taken together, the different BCs vary substantially with respect to their relationship to BV.

A further finding of this analysis is that the different BCs scale differently to BV. Two BCs (Accumbens and NAWM) clearly increase out of proportion with BV. In other words, NAWM and Accumbens increase 'faster' than BV. CC and the Amygdala increase proportionally to BV. The other BCs increase less than proportional to BV, indicating that the relative proportion (related to BV) of these BC measures decreases as BV increases.

These findings fit well with recent reports suggesting that larger brains require relatively more WM because of the large distances for information transmission. Thus, a faster transmission speed is necessary to keep transmission times constant across different brain sizes [3,4,14,34].

Fig. 3



Relative importance of each brain compartment predicting brain volume (BV). Indicated are the important metrics as a percent of the total variance explained by the multiple regression model including all brain metrics in the equation. The vertical lines indicate the 99% confidence intervals estimated on the basis of 5000 bootstrap randomizations. Some of the brain compartmental measures are abbreviated to be used in this figure. Ac, Accumbens; Am, Amygdala; Cau, Caudate; CBGM, cerebellar gray matter volume; CBWM, cerebellar white matter volume; CC, corpus callosum volume; CSA, cortical surface area; CT, cortical thickness; NAWM, cerebral normal-appearing white matter volume; Pa, Pallidum; Pu, Putamen; Th, Thalamus.

To expedite information transfer, more myelin is needed to wrap the association tracts at the end, resulting in a larger volume of cerebral WM.

With the exception of the Amygdala and CC (which vary in proportion to BV), all further BCs increase 'slower' with increasing BV. Larger brains are thus associated with relatively smaller BC volumes. CT is only weakly related to BV, a finding that is partly in contradiction to the results provided by Vouksima *et al.* [35] reporting no relationship. To reconcile our findings with those of Vouksima *et al.* [35], one can state that this relationship is less clear than the relationship of most of the other BCs.

The extreme differences in BV to brain compartment relationships have substantial practical implications. For example, in brain imaging research, MRI measurements of brains are mostly transformed from native space to a standard stereotactic space (MNI or Talairach and Tournoux) [8,36]. These transformations, regardless of whether they use linear or nonlinear transformation functions, do not take into account the different allometric relationships between the individual brain compartments and total BV. A further problem arises when the different brain compartments are normalized to BV, for example, to examine sex differences independent of total BV. Because of the different relationships between the brain compartments and BV, this normalization might either overestimate or underestimate the volumes of the brain compartments, and thus bias the analysis in an unpredictable manner.

As can be seen from Table 2, there are substantial sex differences with respect to the different brain measures [1,5,6,37,38]. This is a well-known fact and has been discussed intensively in several eminent papers. As this paper is not designed to examine anatomical sex differences, we will refrain from discussing this issue in the context of this paper. We point out that several studies have shown that these sex differences strongly diminish or even disappear when the brain measures are normalized to total ICV [1,5]. However, it has to be kept in mind that BV is only imperfectly associated with ICV and that the relation is also less than proportional.

Conclusion

This statistical analysis uncovered extremely different relationships between total BV and the BC metrics. The uncovered relationships varied between an extremely strong relationship (BV explaining 85% of the variability of NAWM volume) to very weak relationships (Caudate and CT). In addition, NAWM and Accumbens scaled out of proportion with BV, whereas most other BC measures scaled less than proportional to BV. Thus, NAWM increases at a faster rate than does BV, with larger brains showing relatively larger NAWM and Accumbens than smaller brains. CortexVol (and most of the other BCs), on the other hand, increases less than BV, resulting in relatively smaller CortexVol in large brains. These different relationships might be linked to specific allometric principles that are mostly unknown. However, we speculate that with increasing brain size, there is a greater need for increased speed of information transfer by the cortical fiber system. Thus, an increase in cerebral WM volume is necessary for larger brains. Taken together the BC volumes do not simply scale up linearly with increasing brain size.

Acknowledgements

The current analysis incorporates data from the Longitudinal Healthy Aging Brain (LHAB) database project, which is carried out as one of the core projects at the International Normal Aging and Plasticity Imaging Center/INAPIC and the University Research Priority Program 'Dynamics of Healthy Aging' of the University of Zurich. The following members of the core INAPIC team were involved in the design, set-up, maintenance, and support of the LHAB database: Anne Eschen, Lutz Jäncke, Mike Martin, Susan Merillat, Christina Rocke, and Jacqueline Zöllig.

Conflicts of interest

There are no conflicts of interest.

References

1 Jäncke L, Mérillat S, Liem F, Hänggi J. Brain size, sex, and the aging brain. *Hum Brain Mapp* 2015; **36**:150–169.
2 Ritchie SJ, Bastin ME, Tucker-Drob EM, Maniega SM, Engelhardt LE, Cox SR, *et al*. Coupled changes in brain white matter microstructure and fluid intelligence in later life. *J Neurosci* 2015; **35**:8672–8682.
3 Lüders E, Steinmetz H, Jäncke L. Brain size and grey matter volume in the healthy human brain. *Neuroreport* 2002; **13**:2371–2374.
4 Hänggi J, Fövenyi L, Liem F, Meyer M, Jäncke L. The hypothesis of neuronal interconnectivity as a function of brain size: a general organization principle of the human connectome. *Front Hum Neurosci* 2014; **8**:915.
5 Leonard CM, Towler S, Welcome S, Halderman LK, Otto R, Eckert MA, *et al*. Size matters: cerebral volume influences sex differences in neuroanatomy. *Cereb Cortex* 2008; **18**:2920–2931.
6 Lemaître H, Crivello F, Grassiot B, Alpérovitch A, Tzourio C, Mazoyer B. Age- and sex-related effects on the neuroanatomy of healthy elderly. *Neuroimage* 2005; **26**:900–911.
7 Schlaug G, Jäncke L, Huang Y, Staiger JF, Steinmetz H. Increased corpus callosum size in musicians. *Neuropsychologia* 1995; **33**:1047–1055.
8 Talairach J, Tournoux P. *Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: an approach to cerebral imaging*. New York, NY: Thieme Medical Publishers Inc.; 1988.
9 Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas ES, Rainey L, *et al*. Automated Talairach Atlas labels for functional brain mapping. *Hum Brain Mapp* 2000; **10**:120–131.
10 Jäncke L. The plastic human brain. *Restor Neurol Neurosci* 2009; **27**:521–538.
11 May A. Experience-dependent structural plasticity in the adult human brain. *Trends Cogn Sci* 2011; **15**:475–482.
12 Zatorre RJ, Fields RD, Johansen-Berg H. Plasticity in gray and white: neuroimaging changes in brain structure during learning. *Nat Neurosci* 2012; **15**:528–536.
13 Jäncke L, Staiger JF, Schlaug G, Huang Y, Steinmetz H. The relationship between corpus callosum size and forebrain volume. *Cereb Cortex* 1997; **7**:48–56.
14 Ringo JL, Doty RW, Demeter S, Simard PY. Time is of the essence: a conjecture that hemispheric specialization arises from interhemispheric conduction delay. *Cereb Cortex* 1994; **4**:331–343.
15 Zöllig J, Mérillat S, Eschen A, Röcke C, Martin M, Jäncke L. Plasticity and imaging research in healthy aging: core ideas and profile of the International Normal Aging and Plasticity Imaging Center (INAPIC). *Gerontology* 2011; **57**:190–192.
16 Valizadeh SA, Hänggi J, Mérillat S, Jäncke L. Age prediction on the basis of brain anatomical measures. *Hum Brain Mapp* 2017; **38**:997–1008.
17 Hirsiger S, Koppelmans V, Mérillat S, Liem F, Erdeniz B, Seidler RD, *et al*. Structural and functional connectivity in healthy aging: associations for cognition and motor behavior. *Hum Brain Mapp* 2016; **37**:855–867.
18 Madhyastha T, Mérillat S, Hirsiger S, Bezzola L, Liem F, Grabowski T, *et al*. Longitudinal reliability of tract-based spatial statistics in diffusion tensor imaging2014; **35**:4544–4555.
19 Valizadeh SA, Liem F, Mérillat S, Hänggi J, Jäncke L. Identification of individual subjects on the basis of their brain anatomical features. *Sci Rep* 2018; **8**:5611.
20 Seidler R, Erdeniz B, Koppelmans V, Hirsiger S, Mérillat S, Jäncke L. Associations between age, motor function, and resting state sensorimotor network connectivity in healthy older adults. *Neuroimage* 2015; **108**:47–59.
21 Koppelmans V, Hirsiger S, Mérillat S, Jäncke L, Seidler RD. Cerebellar gray and white matter volume and their relation with age and manual motor performance in healthy older adults. *Hum Brain Mapp* 2015; **36**:2352–2363.
22 Muller AM, Merillat S, Jancke L. Older but still fluent? Insights from the intrinsically active baseline configuration of the aging brain using a data driven graph-theoretical approach. *Neuroimage* 2016; **127**:346–362.
23 Folstein MF, Folstein SE, McHugh PR. Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**:189–198.
24 Annett M. A classification of hand preference by association analysis. *Br J Psychol* 1970; **61**:303–321.
25 Sturm W, Horn W, Willmes K. *Leistungsprüfsystem für 50-90jährige:(LPS 50+); Handanweisung (engl., Performance testing system for 50 to 90 year olds)*. Göttingen: Hogrefe, Verlag für Psychologie; 1993.
26 Destrieux C, Fischl B, Dale A, Halgren E. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage* 2010; **53**:1–15.
27 Fischl B, Salat DH, van der Kouwe AJ, Makris N, Segonne F, Quinn BT, *et al*. Sequence-independent segmentation of magnetic resonance images. *Neuroimage* 2004; **23** (**Suppl 1**):S69–S84.
28 Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, *et al*. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 2002; **33**:341–355.
29 Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, *et al*. Automatically parcellating the human cerebral cortex. *Cereb Cortex* 2004; **14**:11–22.
30 Khan IN. *Sex differences and the effects of sex hormones on the structure of the corpus callosum [PhD thesis]*. Nottingham: University of Nottingham; 2012.
31 Reiss MJ. *The allometry of growth and reproduction*. Cambridge: Cambridge University Press; 1991.
32 Grömping U. Relative importance for linear regression in R: the package relaimpo. *J Stat Softw* 2006; **17**:1–27.
33 Core Team R. *R: a language and environment for statistical computing*. Vienna: R Foundation for Statistical Computing; 2013.
34 Jäncke L, Preis S, Steinmetz H. The relation between forebrain volume and midsagittal size of the corpus callosum in children. *Neuroreport* 1999; **10**:2981–2985.
35 Vuoksimaa E, Panizzon MS, Chen CH, Fiecas M, Eyler LT, Fennema-Notestine C, *et al*. The genetic association between neocortical volume and general cognitive ability is driven by global surface area rather than thickness. *Cereb Cortex* 2015; **25**:2127–2137.
36 Evans AC, Janke AL, Collins DL, Baillet S. Brain templates and atlases. *Neuroimage* 2012; **62**:911–922.
37 Ingalhalikar M, Smith A, Parker D, Satterthwaite TD, Elliott MA, Ruparel K, *et al*. Sex differences in the structural connectome of the human brain. *Proc Natl Acad Sci USA* 2014; **111**:823–828.
38 Joel D, Berman Z, Tavor I, Wexler N, Gaber O, Stein Y, *et al*. Sex beyond the genitalia: the human brain mosaic. *Proc Natl Acad Sci USA* 2015; **112**:15468–15473.